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The efficacy of low- and high-molecular-weight hyaluronic acid applications after arthroscopic debridement in patients with osteoarthritis of the knee

Gonartrozlu hastalarda artroskopik debridman sonrası düşük ve yüksek molekül ağırlıklı hiyalüronik asit uygulamalarının etkinliği

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Amaç: Diz osteoartriti tanısıyla artroskopik debridman (AD) sonrasında düşük veya yüksek molekül ağırlıklı hiyalüronik asit (HA) enjeksiyonu uygulanan hastalarda viskosuplementasyonun etkinliği değerlendirildi.

Çalışma planı: Çalışmaya, Kellgren-Lawrence ölçütlerine göre evre 2 veya 3 diz osteoartriti tanısı konan 45 hasta (19 erkek, 26 kadın; ort. yaş 53; dağılım 41-66) alındı. Hastalar AD sonrasında §rastgele üç gruba ayrıldı. Synvisc grubuna (n=16) 2 ml Hylan G-F 20 birer hafta arayla üç kez, Hyalgan grubuna (n=14) 2 ml sodyum hiyalüronat birer hafta arayla beş kez eklem içine uygulandı. Kontrol grubuna (n=15) ise enjeksiyon uygulaması yapılmadı. Tüm hastalar ameliyat öncesinde ve ameliyat sonrası 6. ve 12. aylarda ağrı, eklem sertliği ve fiziksel fonksiyon açısından WOMAC (Western Ontario and McMaster Universities) osteoartrit indeksi ile değerlendirildi.

Sonuçlar: Synvisc grubunda iki, Hyalgan grubunda üç hastada enjeksiyon sırasında geçici ağrı görüldü. Ameliyat öncesi ile karşılaştırıldığında, ameliyat sonrası 6. ay ve 12. ay WOMAC skorları tüm gruplarda düşüş gösterdi. Altıncı ayda WOMAC skorlarındaki düzelme açısından gruplar arasında fark saptanmazken, 12. ayda elde edilen düzelme farkı hem Synvisc hem de Hyalgan gruplarında kontrol grubuna göre anlamlı derecede fazlaydı (sırasıyla p=0.004 ve p=0.003); ancak, Synvisc ve Hyalgan grupları arasında bu açıdan fark yoktu (p>0.05).

Çıkarımlar: Bulgularımız, gonartrozlu olgularda uygun endikasyonlarda AD'nin yararlı olduğunu, sonrasındaki viskosuplementasyon uygulaması ile tedavi etkinliğinin arttığını ve etkinlik açısından yüksek ve düşük molekül ağırlıklı HA preparatları arasında fark olmadığını göstermektedir.

Anahtar sözcükler: Artroskopi; debridman; hiyalüronik asit/terapötik kullanım; enjeksiyon, eklemiçi; osteoartrit, diz/tedavi.

Objectives: We evaluated the efficacy of viscosupplementation with low- or high-molecular-weight hyaluronic acid (HA) preparations following arthroscopic debridement (AD) in patients with osteoarthritis of the knee.

Methods: The study included 45 patients (19 men, 26 women; mean age 53 years; range 41 to 66 years) with Kellgren-Lawrence grade 2-3 osteoarthritis of the knee. Following AD, the patients were randomized to three groups to receive three intra-articular injections of 2 ml hylan G-F 20 (Synvisc, n=16), five intra-articular injections of 2 ml sodium hyaluronate (Hyalgan, n=14), and no injections (controls, n=15). Injections were administered at one-week intervals. All the patients were evaluated with pain, stiffness, and functional capacity scores of the WOMAC (Western Ontario and McMaster Universities) osteoarthritis index before and 6 and 12 months after AD.

Results: Two patients and three patients complained of transient pain in Synvisc and Hyalgan groups, respectively. WOMAC scores showed significant decreases in all the groups at 6 and 12 months. There were no significant differences between the three groups with respect to improvement in WOMAC scores at 6 months. However, compared to the control group, differences between pre- and posttreatment scores at 12 months were significantly greater in the Synvisc (p=0.004) and Hyalgan (p=0.003) groups, with no significant difference between the two HA groups (p>0.05).

Conclusion: Our findings show that AD is beneficial in osteoarthritis of the knee in patients with appropriate indications, viscosupplementation increases the efficacy of treatment, and that low- and high-molecular-weight HA preparations have similar efficacy.

Key words: Arthroscopy; debridement; hyaluronic acid/therapeutic use; injections, intra-articular; osteoarthritis, knee/therapy.

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Some problems in osteoarthritis treatment still remain unsolved in today's clinical management as in the past. Analgesic agent administration, physiotherapy and viscosupplementation constitute the first step in treatment of OA and when these are not enough, surgical interventions such as arthroscopic debridement (AD) comes into consideration.[1,2] It has been reported that the mean favorable outcome rates achieved from surgical treatment of gonarthrosis are between 33,3 and 80 percent in 1 to 10 years period.[3] In recent years, intra-articular hyaluronic acid injection treatment takes more place in clinical practice. [4] It has been reported that intra-articular hyaluronic acid treatment resulted in positive outcome following 3 to 12 months after the treatment.[3] Currently, there are two types of hyaluronic acid preparations: Low and high molecular weight. The latter have relatively better results [5] In gonarthrosis treatment with AD, generally analgesic agents and supportive physiotherapy are used. Good results have been reported from studies conducted on the effects of intra-articular hyaluronic acid following arthroscopic debridement[1,3,6-9] However, we did not find any controlled study which aims to compare the viscosupplementation results established from the patients treated with various hyaluronic acid preparations of different molecular weights in the literature. In this prospective study, we aimed to evaluate the clinical outcomes of viscosupplementation application added to treatment following AD surgery and to compare the effects of low and high molecular weight hyaluronic acid preapartions on the given results.

Patients and method

A total of 45 patients (19 males and 26 females) diagnosed as having knee osteo arthritis according to the criteria of ACR (American College of Rheumatology), who still remained untreated even after a three months of conservative treatment were included in this study. The main age of the participants were 53 and the age range was between 41 and 66 years. The knee joints (27 right and 18 left) of the patients were examined. Preoperative evaluation was performed via taking radiographic images of the knee joint and patellar bone enforced by a load from anteroposterior, lateral and tangential aspects according to the criteria of Kellgren-Lawrence.[4] In all patients, there was an osteoarthritis manifestation at stage II or III. In patients with bilateral gonarthrosis, the knee with more pain was evaluated. For this study, the exclusion criteria were as follows: Patients with allergic disorder, oral or intramuscular corticosteroid agent administration history in last two months, individuals who have severe systemic disorders, intra-articular therapy history to the evaluated knee in last three months or arthroscopic intervention history in last three years. A written approval consent has been provided from the Local Ethical Committee of the Süleyman Demirel University prior to the study. The study was designed in a blinded, randomized and controlled fashion. All patients were undergone AD intervention under general anesthesia. Following the surgical operation, the patients were seperated into three groups: Synvisc group (n=16), Hyalgan group (n=14) and controls (n=15). Each patient was only given an envelope which includes a number showing a number representing the treatment type and none of the participants was told which kind of treatment was they were administered. After the AD operation, Hylan G-F 20 at 2 ml dose was administered once a week for three weeks to Synvisc group, whereas sodium hyaluronate at 2 ml dose was given to Hyalgan group once a week for five weeks. Control group did not receive any injection treatment following AD. After the surgery, all patients were applied compressive elastic bandage, active quadriceps exercise and continuous passive motion program. Also, tiaprofenic acid (Surgam Aventis, Turkey) treatment was initiated for all subjects. Patients were discharged from the hospital after three days from the operation with a home exercise programme. All participants were evaluated before and 6 / 12 months after the operation by means of pain, joint stiffness and physical function via using WOMAC (western Ontario and McMaster Universities) Index For Osteoarthritis. Systematical and local adverse effects of treatment were recorded. Data were

Table 1. Comparison of the patient groups by means of age and body mass index*

	Synvisc (n=16)	Hyalgan (n=14)	Controls (n=15)	*p*
Age (Years)	53.0±6.2	53.4±5.0	53.1±6.9	0.981
Body Mass Index (kg / m^2)	29.6±5.7	31.7±5.1	27.5±5.3	0.108

*: Kruskal-Wallis test.

Table 2. Distribution of WOMAC scores in study groups.

	Synvisc (n=16)	Hyalgan (n=14)	Controls (n=15)	*p*
Preoperative	67.6±22.5	100.3±9.9	70.7±21.2	0.000
Postoperative (6 mopnths)	60.3±25.5	92.7±13.3	65.5±23.0	0.001
Postoperative (12 mopnths)	53.3±23.7	86.8±11.2	63.3±20.8	0.001

represented as mean and standart deviation. In statistical analysis, Mann-Whitney U and Kruskall-Wallis tests were used for non-parametric in and between group comparisons via using SPSS 11 for Windows. P values less than 0.05 were considered as significant.

Results

There was no difference between the groups by means of age and body mass index ($p > 0.05$) (Table-1). WOMAC score results are given in Table-2. Postoperative WOMAC scores were prominently lower in whole groups, when compared with the scores established prior to the operation. There was a statistically significant difference in WOMAC scores measured before the operation and 6 / 12 months after the operation ($p=0.000$, $p=0.001$ and $p=0.001$ respectively). As there was a significant difference in preoperative WOMAC scores, improvemet rates in WOMAC values were calculated for each group in order to evaluate the efficiency of AD operation applied in combination with viscocupplementation treatment (Table-3). There was a significant decrease especially in WOMAC scores recorded at 12th month (Table-3) and this difference was present for both Synvisc and Hyalgan groups, when compared with the controls ($p=0.004$ and $p=0.003$ respectively). But, there was no significant difference between tyhe Synvisc and Hyalgan groups ($p=0.616$).

Discussion

In many studies, it has been emphasized it is very crucial to select a suitable patient population for AD and intra-articular HA treatment. Both treatment methods have been reccomended for patients with mild or moderate gonarthrosis and it has also been reported that these treatment modalities could yield different outcomes in short and log terms.[2,5,8,10,11] In our study, we have especially paid attention to include the participants who are at stage 2 and 3 according to Kellgren-Lawrence criteria and who are in or near the same age and body mass index ranges, so that homogenity of group distributions and requirement for gonarthrosis cases at mild to moderate degrees have been fulfilled. In patients with gonarthrosis who have undergone AD operation in suitable indications, approximately 80 percent of recovery is established.[1,3] Debridement and lavage interventions can lead to a recovery in symptomatical level, but these can not interfere with the progression of disease.[12] Elmalı et al. have reported that the favorable outcomes of AD mostly seen in suitable cases and in gonarthrosis at early stages.[13] Clarke and Scott have reported that 66 percent of the patients who have severe gonarthrosis experienced recovery while they were at moderate stage, whereas Fond et al. have stated that a 70 percent of recovery rate was achieved in AD treatment in five years.[15]

Whereas, in a controlled study by Moseley et al., it has ben reported that there was no difference among the groups treated with AD, arthroscopic lavage and placebo surgery by means of pain relieve and functional improvement.[16] In our study, there was a significant decrease in WOMAC scores during 6th and 12th months, which suggest the favorable effect of AD. Viscosupplementation treatment contributes to the elasticity and viscosity of synovial fluid, thereby ameliorating the protection, lubrication and shock absorbing effects, as well as tissue regeneration.[17,18] Symptomatic effect of this method begins 3-5 weeks after the initiation of therapy and generally lasts for

Table 3. Difference of improvement rates in postoperative WOMAC scores, compared to those of the preoperative values.

	Synvisc	Hyalgan	Controls	*p*
Difference of pre and post operative states				
Postoperative (6 months)	7.3±6.3	7.6±4.7	5.2±3.8	0.538
Postoperative (12 months)	14.3±7.0	13.5±5.2	7.5±4.6	0.004

more than one year.[12] There are numerous studies supporting intra-articular hyaluronic acid treatment and good outcomes have been reported between 3 and 12 months in clinical trials.[3] In another study conducted by Koyuncu et al. on 17 patients with primary gonarthrosis, it has been reported that 51.1, 53 and 70.5 percent of good outcome rates were achieved respectively one week, two weeks after the study and during the last follow-up controls.[18] In the same study, it has also been emphasized that three weeks of injection treatment was perfectly tolerated in parallel to pain relieve, decrement in WOMAC, Lequesne and SF-36 scores and having no adverse effect. Ate_ et al. have stated that there is a significant recovery in all pain and function scores except night pain in patients followed for 21 weeks.[19]

Whereas in another double-blinded and randomized study by Jones et al., it has been reported that there was no significant difference between the intra-articular hyaluronic acid given and triamcinolone injected patient groups with gonarthrosis by means of joint stiffness, joint motion gap, effusion, local heat, tenderness, synovial viscosity increment and pain levels during a six months of follow-up period.[20] In our study, it was impossible to make an evaluation or interpretation for the effects of solely intra-articular hyaluronic acid treatment, as there was no patient group which was only treated with viscosupplementation in our study. Despite this fact, the significance of recovery in WOMAC scores of Synvisc and Hyalgan given groups 12 months after the operation indicated that viscosupplementation treatment applied in combination with AD is a favorable approach.

Yet, there are few papers in the literature in which the outcomes of AD plus viscosupplementation treatment is evaluated. Listrat et al. have reported that there was less structural deterioration in study group treated with Hyalgan after arthroscopic lavage operation, when compared with the controls.[9] In the same study, it has also been mentioned that Hyalgan was more beneficial for mean life quality and there was less need to use analgesig agents in this group. In their study in which 57 knee joints with chondral lesions at stages 1 to 4 according to the Oterbridge Scoring were treated with sodium hyaluronate followign arthroscopic lavage and shaving operations and subsequently evaluated according to the Lysholm Scoring System at 6th and 22nd months after the operation, Akman et al. have reported that intra-articular hyaluronic acid injection was found to be effective by means of functional stability and pain relief, however this could not stand so long.[3] Elmalı et al. have applied intra-articular sodium hyaluronate injection treatment once for a week for three weeks after AD surgery and evaluated the patients 12 amd 20 months following the treatment according to the knee scoring of Hospital for Special Surgery and Knee Society Scoring System. In this follow-up study, it has been reported that the recovery rates were 79.3 and 69 at 12th and 20th months respectively and it has also been summarized that hyaluronic acid injection was found to be beneficial.[1]

Vad et al. have compared the group treated with combined therapy of closed lavage and intra-articular Hylan G-F 20 and the group only treated with only Hylan G-F 20 and concluded that combined therapy has had beter outcome during a 1.1 year follow-up.[7] In another study by Uluçay et al., in which they have evaluated 77 female patients and seperated them into three groups, patient groups were then treated with intra-articular viscosupplementation of sodium hyaluronate, streptococcal hyaluronate and Hylan G-F 20 once a week for three weeks following arthroscopic treatment.[8] They have reported that high levels of recovery was established with combined arthroscopy and viscosupplementation treatment and whole used preparations have no superioriority to each other. The results achieved from our study was in accordance with the previous studies that intra-articular hyaluronic acid injection following AD operation have favorable effects on symptomatic manifestations of gonarthrosis. However, only the clinical outcomes have been pointed out in the mentioned studies and there is no sufficient data on comparison of different agents used in viscosupplementation treatment.[1,3,8,9]

Although there is a comparison in the study of Ulucay et al.[8], it is worth paying attention to the absence of the control group and shortness of the study duration. In our study, improvement in WOMAC scores of Synvisc and Hyalgan groups were prominent 12 months after the operation, when compared with the controls. This result suggests that intra-articular hyaluronic acid treatment applied in combination with AD operation have more beneficial effects than AD surgery alone. As there was also a difference between the groups by means of WOMAC scores prior to the operation, recovery difference values were used instead of WOMAC scores for subsequent group

comparisons following the surgery. We think that this may reflect the results of our study more accurate. Hyaluronic acid preparations are classified as having low (0.5 to 2 million Daltons) and high (6 to 7 million Daltons) molecular weight. Though vast majority of the papers in the literature are focused on the more beneficial effects of hyaluronic acid with high molecular weight, there are also some studies reporting there is no difference between the two types of hyaluronate by means of treatment outcomes.[21] In a randomized and controlled study in which hyaluronic acid preparations with low and high molecular weights were compared, the high molecular weight hyaluronic acid have significantly more impact on pain relief during a 12 weeks of follow-up.[22] Wobig et al. have compared preparations with high molecular weight hyaluronate and reported that Hylan G-F 20 was beter in pain control and phsical function aspects.[17]

In a meta-analysis study by Wang et al., it has been reported that high molecular weight preparation injection including cruciate ligaments have better outcomes than low molecular weight preparation injection not including cruciate ligaments.[5] Whereas in another double-blinded, randomized and controlled study conducted on 184 knee joints of 92 patients with osteoarthritis by Karatosun et al, it has been reported that low and high molecular weight treatment modalities were both effective on pain relief and functional recovery and there was no difference between these two treatment types.[23] In our study, there was no statistically significant difference between the low (0.50-0.73 million Daltons) and high (6 million Daltons average) molecular weight sodium hyaluronate injection treatments by means of improvement achieved in WOMAC scores 12 months after AD intervention, which in turn suggests that preparations with high and low molecular weight have no superior aspect to each other, supporting the results gained from other studies in this way. In clinical trials, it has been stated that intra-articular hyaluronic acid injection treatment has mostly local side effects, with temporary pain and sweating are the most observed ones. There are various side effect rates. For instance: Puttick et al. have reported a 27 percent of local adverse effect rate associated with intra-articular hyaluronic acid injection, whereas Lussier et al. habe reported an 8.3 percent rate.[21,24] Beks et al. reported that hyaluronate treatment has no systematical side effect.[25] In our study, we did not observe any systematical adverse effect and local side effect rate was 11.1 percent, which was in accordance with the literature.

As a result of this study, we conclude that AD is a beneficial treatment method in case of suitable indications and viscosupplementation contributes to the efficiency of treatment. Our results indicate that hyaluronic acid preparations with low and high molecular weight have no superiority to each other in ameliorating gonarthrosis symptoms. However, when it is taken into consideration that comparison studies are generally focused on gonarthrosis patients who have not been undergone surgical intervention yet, one should keep in mind that AD operation may lead to some alterations in pathogenetical mechanisms which underlies the symptoms of gonrathrosis, thereby cause a difference in outcomes of hyaluronic acid treatment approaches between operated and unoperated joints. For this reason, some issues such as whether heyaluronic acid treatment is necessary following an arthroscopic intervention to knee and if so, which hyaluronic acid type should be preffered requie more comprehensive clinical, radiological and biological studies in order to be elucidated clearly. We hope our study constitute an insight or step into this kind of studies.

References

1. Elmalı N, İnan M, Ertem K, Esenkaya İ, Ayan İ, Karakaplan M. Diz osteoartritinin artroskopik debridman ve intraartikuler hyaluronik asit ile tedavisi. Artroplasti Artroskopik Cerrahi Dergisi 2002;13:131-5.
2. Orkun S. Osteoartrit tedavisinde yenilikler. Aktüel Tıp Dergisi 2004:9:26-9.
3. Akman S, Sen C, Gogus A, Demirhan M, Kilicoglu O. The efficacy of intraarticular sodium hyaluronate injection following arthroscopic debridement in the treatment of gonarthrosis. [Article in Turkish] Acta Orthop Traumatol Turc 2001;35:107-10.
4. Keser S, Bayar A, Tuncay İ, Ege A, Demirel N. Osteoartritli dizlerde intraartiküler hyaluronik asit enjeksiyon sonuçları. Romatizma 2004;19:173-7.
5. Wang CT, Lin J, Chang CJ, Lin YT, Hou SM. Therapeutic effects of hyaluronic acid on osteoarthritis of the knee. A meta-analysis of randomized controlled trials. J Bone Joint Surg [Am] 2004;86:538-45.
6. Satana T, Sarban S. Ergüven M, Atik Ş. Gonartroz tedavisinde artroskopik debridman ve viskosuplementasyon uygulamalarının klinik sonuçları. In: 18. Milli Türk Ortopedi ve Travmatoloji Kongresi Kitabı; 18-23 Ekim 2003; İstanbul, Türkiye. 2003. s. 75.
7. Vad VB, Bhat AL, Sculco TP, Wickiewicz TL. Manage-

ment of knee osteoarthritis: knee lavage combined with hylan versus hylan alone. Arch Phys Med Rehabil 2003; 84:634-7.

8. Ulucay C, Altintaş F, Ugutmen E, Beksac B. The use of arthroscopic debridement and viscosupplementation in knee osteoarthritis. [Article in Turkish] Acta Orthop Traumatol Turc 2007;41:337-42.
9. Listrat V, Ayral X, Patarnello F, Bonvarlet JP, Simonnet J, Amor B, et al. Arthroscopic evaluation of potential structure modifying activity of hyaluronan (Hyalgan) in osteoarthritis of the knee. Osteoarthritis Cartilage 1997;5:153-60.
10. Sarban S, Satana T, Işıkan E. Diz osteoartritinde viskosuplementasyonun yeri. Aktüel Tıp Dergisi 2004:9:30-4.
11. Dıraçoğlu D. Osteoartritte intraartiküler hyalüronik asit tedavisi. Türk Fiz Tıp Rehab Derg 2007;53:154-9.
12. Haq I, Murphy E, Dacre J. Osteoarthritis. Postgrad Med J 2003;79:377-83.
13. Elmalı N, Ertem K, İnan M, Ayan İ, Esenkaya İ, Karakaplan M. Diz dejeneratif artritinin artroskopik tedavisi. İnönü Üniversitesi Tıp Fakültesi Dergisi 2001;8:5-8.
14. Clarke HD, Scott WN. The role of debridement: through small portals. J Arthroplasty 2003;18(3 Suppl 1):10-3.
15. Fond J, Rodin D, Ahmad S, Nirschl RP. Arthroscopic debridement for the treatment of osteoarthritis of the knee: 2- and 5-year results. Arthroscopy 2002;18:829-34.
16. Moseley JB, O'Malley K, Petersen NJ, Menke TJ, Brody BA, Kuykendall DH, et al. A controlled trial of arthroscopic surgery for osteoarthritis of the knee. N Engl J Med 2002;347:81-8.
17. Wobig M, Bach G, Beks P, Dickhut A, Runzheimer J, Schwieger G, et al. The role of elastoviscosity in the efficacy of viscosupplementation for osteoarthritis of the knee: a comparison of hylan G-F 20 and a lower-molecular-weight hyaluronan. Clin Ther 1999;21:1549-62.
18. Koyuncu H, Uludağ M, Çakmak B, Yücel E, Dinç A, Toros H ve ark. Diz osteoartritinde Hylan G-F 20'nin etkinlik ve tolerabilitesi. Hipokrat Lokomotor 2005;6:277-81.
19. Ateş A, Kınıklı G, Turgay M, Duman M. Diz osteoartritli hastalarda sodyum hyaluronat ile viskosuplementasyon tedavisinin etkinliği. Türk Geriatri Dergisi 2004;7:21-4.
20. Jones AC, Pattrick M, Doherty S, Doherty M. Intra-articular hyaluronic acid compared to intra-articular triamcinolone hexacetonide in inflammatory knee osteoarthritis. Osteoarthritis Cartilage 1995;3:269-73.
21. Puttick MP, Wade JP, Chalmers A, Connell DG, Rangno KK. Acute local reactions after intraarticular hylan for osteoarthritis of the knee. J Rheumatol 1995;22:1311-4.
22. Jordan KM, Arden NK, Doherty M, Bannwarth B, Bijlsma JW, Dieppe P, et al. EULAR Recommendations 2003: an evidence based approach to the management of knee osteoarthritis: Report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). Ann Rheum Dis 2003; 62:1145-55.
23. Karatosun V, Unver B, Gocen Z, Sen A. Comparison of two hyaluronan drugs in patients with advanced osteoarthritis of the knee. A prospective, randomized, double-blind study with long term follow-up. Clin Exp Rheumatol 2005;23:213-8.
24. Lussier A, Cividino AA, McFarlane CA, Olszynski WP, Potashner WJ, De Medicis R. Viscosupplementation with hylan for the treatment of osteoarthritis: findings from clinical practice in Canada. J Rheumatol 1996;23:1579-85.
25. Beks P, Dickhut A, Maicr R, Scale D, Vettur G, Wobig M, Wolpert W. Viscosupplementation with Synvisc: Efficacy and safety studies in the osteoarthritic knee. In: A compilation of clinical studies to be published: Viscosupplementation: a new treatment for osteoarthritis. Ridgefield, NJ: Biomalrix Inc.; 1996.